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THE REGRESSIVE TREND OF COMPLEX PHENOTYPIC STRUCTURES IN NEUTRAL EVOLUTION

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The Regressive Trend of Complex Phenotypic Structures in Neutral Evolution. Dzeverin I. I. — Evolutionary changes of characters formed in ontogeny by developmental induction are modeled for an infinite population and for replicate finite populations under a mutation — drift equilibrium. Induction occurs by interaction of reactants, which must therefore coincide in time intervals of their abilities to react. This mechanism is being damaged in evolution of useless structures by random mutations in genes that control simultaneous formations of reactants, whereas mutational effects on important structures are restrained by selection. The breakdown of induction mechanisms produces increased variability and degeneration in vestigial characters. Quantitative estimations are illustrated by data regarding regressive trends in some groups of mammals. Time spans sufficient for complete loss of vestigial organs obtained from the modelings are much smaller than the periods of macroevolutionary changes. Certain functional value and the genetic correlation with important structures are the most probable mechanisms that could prevent the rapid loss of vestigial structures.

Key words: vestigial organ, threshold character, quantitative character, developmental induction, neutral evolution, regressive evolution, morphometric variation, mammals.

Регрессивный тренд сложных фенотипических структур в нейтральной эволюции. Дзеверин И. И. — Математические модели эволюционных изменений признаков, формирующихся в онтогенезе путем индукции, разработаны для бесконечной популяции, а также для группы конечных популяций, находящихся в состоянии равновесия между мутационным процессом и генетическим дрейфом и имеющих одинаковые исходные свойства. В норме индукция происходит вследствие взаимного влияния специфических реагентов, которые должны, следовательно, формироваться в онтогенезе одновременно. В эволюции бесполезных структур этот механизм нарушается случайными мутациями в генах, контролирующих сроки развития реагентов, а в эволюции структур, нужных организму, накопление мутаций сдерживается естественным отбором. Нарушения механизмов индукции становятся причиной увеличения изменчивости и упрощения строения рудиментарных органов вплоть до полной их утраты. Количественные модели этих процессов проиллюстрированы данными о регрессивных трендах в эволюции морфологических признаков в некоторых группах млекопитающих. Моделирование показало, что отрезок времени, достаточный для полной утраты рудиментарных органов, намного меньше, чем обычные периоды макроэволюционных изменений. Некоторое функциональное значение и генетическая корреляция с важными структурами — наиболее вероятные механизмы, которые могут предотвратить быструю потерю рудиментов.

Ключевые слова: рудиментарный орган, пороговый признак, количественный признак, онтогенетическая индукция, нейтральная эволюция, регрессивная эволюция, морфометрическая изменчивость, млекопитающие.

Introduction

Various mechanisms by which complex polygenic phenotypic structures can be established, maintained, and transformed in evolution are learned from the empirical data on evolutionary dynamics of characters. Due to these mechanisms some structures become vestigial and disappear in the evolution course, while others become more complex and more reliable. Organs and systems of organs are examples of such structures.

This paper concerns the dynamics of diminishing the useless organs in evolution frequently ending up with a complete loss of them. My task is to describe the neutral evolution of complex phenotypic structures taking into account both their polygenic determination and developmental events by which such structures are formed in ontogeny. I hope this class of models may be useful as a first approximation for various problems in phenotypic evolution.

Theoretical Background

An array of authors have investigated regressive trends of various organs in all main groups of plants and animals (Sewertzoff, 1939, 1945; Schmalhausen, 1982; Simpson, 1944; Yablokov, 1966; Schemmel, 1984; Parzefall, 1984; Peters, Peters, 1984; Dzwillo, 1984; Jeffery, 2001 et al.). Good examples of regressive trends can be revealed from the evolution of dental characters in mammals, for example, Chiroptera (Menu, 1985, 1987; Wołoszyn, 1987) and Primates (Zubov, Khaldeyeva, 1989), or from the limb losses in various groups of vertebrates (Lande, 1978).

As a rule, the patterns of evolutionary regressive transformations are rather similar for various organs in different groups. Degenerating, an organ gradually decreases in size, its variability increases, and the structure becomes more simple. Thus, only a vestigial structure with obvious features of under-development remains. Eventually the organ disappears, however occasionally it can develop in some individuals of a population as an atavistic structure, even after a rather long period of time. The reverse evolution of a degenerated organ can occur in some lineages. The rate of regressive transformation can differ in various lineages, as well as a sequence of stages of regression. Very often this sequence is opposite to the sequence of their formation in ontogeny and the suggested sequence of their first emergence in evolution. During each period of its history a large taxon is represented by a number of lineages with similar trends of evolutionary transformations, and so various stages of under-development can be revealed in simultaneously existing species. After a very long period of time the complete loss of a structure can be achieved by the majority or by all species of the taxon.

Regressive trends can be associated with the changes in the patterns of variation. Darwin had assumed that the lack of selection pressure on unused structures leads to the increase of their variability (Darwin, 1872, cited after the re-edition: Darwin, 1998). Developing this hypothesis, Schmalhausen (1938, cited after the re-edition: Schmalhausen, 1982) supposed that the cessation of selection, which had been keeping a certain structure unchanged, results in an unlimited accumulation of random mutations. Since any newly introduced mutation changes development in an arbitrary direction independently of any other mutation, as well as changing the performance of the current genotype, disintegration of an organ and the accumulation of pattern deformations in development should arise. Diminution, simplification, decreasing correlation between parts of this organ, increasing variability, and, finally, the complete loss of the organ are the consequences of these deformations.

Another probable explanation for regressive evolution is that it can be caused by negative selection on harmful features. For certain cases it is possible to associate observed changes with selection on combinations of genes determining size decrease, or deceleration of development, or both of these processes, while in other cases the selection of suppressors of morphogenesis is probable (Lande, 1978). Some classical examples of regressive evolution (in particular, a loss of lateral fingers and toes in evolution of horses, or limb loss in snakes) can be explained as the results of negative selection. Besides, in many cases reduced and simplified organs can be regarded as important adaptations for certain organisms, and selection is supposed to tend to simplify their structure according to this importance (Yablokov, 1966; Zander, 1984).

For many other regressive processes the adaptive significance remains unknown or unproved. Depigmentation and eye loss in speleobionts are well-known examples. Eyes may be useless for cave animals but it has not been proved that they are harmful. This concerns also the final stages of regressive evolution, when the vestigial organ is already so small, that it can not be substantially deleterious. Adaptive explanations can be constructed for such trends too (for example, explaining them by the saving of material), but for all such cases the quantitative examination for input of such changes to fitness is necessary. In certain cases it is possible to explain regressive processes by indirect selection. Various regressive processes can be induced either by negative selection or by mutation accumulation (Schemmel, 1984). A combination of mutation and selection effects seems to be possible too.

A problem with mutational explanation for regressive evolution arises in the quantitative analyses of the dynamics of gene frequencies. It has been shown that under selective neutrality the mean value of a polygenic character in a large population should drift in arbitrary direction while its variance should increase linearly with time (Kimura, 1965; Lande, 1976 a, b). In other words, the termination of selection itself can produce an increase of organ variability, but not the directed change. The decrease of an organ doesn't seem to be more probable during neutral evolution than its increase. Therefore, the long regressive evolution, as a result of which an organ can be completely lost without any input of negative selection, is hardly probable. The possibility for such a trend needs an explanation from the genetic standpoint.

Some vestigial organs were studied genetically. It has been shown that they do not differ in the pattern of genetic determination from other polygenic structures (Wilkens, 1984; Villwock, 1984). Multiple genes control their regression (Jeffery, 2001). Therefore, quantitative genetic techniques seem to be appropriate in the study of their evolution. The modeling presented here is based on quantitative genetic approaches to the study of evolution (review: Falconer, 1985) with introducing the information about some developmental

events. These approaches were successfully applied to analyze the interface between development and evolution (Lande, 1979; Riska, 1986, 1989; Wagner, 1988; Wagner et al., 1997; Gavrilets, Hastings, 1994 etc.)

Any structure or character formed by interaction of pre-existing structures in ontogeny is regarded in this paper as a complex structure or character (with putting more precise definition of complexity off for the future). An organ or any other complex morphological structure initialized in ontogeny by an induction process can be an example of such a structure. The variation of formation patterns is analyzed here for an example of the durations of the abilities of reactants to take part in induction. Apparently it is the most common example of hereditary variability of developmental processes (Schmalhausen, 1982; Korochkin, 2002). A common effect for many mutations is the shift in time of the realization of some reactions in a developing organism (Schmalhausen, 1982; Korochkin, 2002). Some models linking genetic and morphological variation were proposed for developmental inductions, in particular induction effects in mammalian teeth development (Salazar-Ciudad, Jernvall, 2004).

The Quantitative Model

Assume that an organizer becomes competent to influence responding tissue at the moment X_1 and preserves this ability during an interval of time C_1. Assume further, that the responding tissue becomes competent to develop after being influenced by the organizer at the moment X_2 and preserves this ability during an interval of time C_2. Variable $X = X_1 - X_2$ (that is an interval of time between the moments, when the responding tissue and organizer become able to enter a morphogenetic reaction) can be considered as a quantitative measure of coordination in the development of two reactants. Values of duration in the organizer and responding tissue competence, C_1 and C_2, are supposed in this paper to be constant in all specimens of investigated populations during all the modeled period of evolution.

The differentiation process begins, if simultaneously during some interval of time both the organizer is able to trigger a reaction, and the responding tissue is able to react. If the formations of these reactants do not coincide in time, the induction becomes impossible. It is supposed here, that the induction follows the all-or-nothing pattern, that is the differentiation process either is realized completely, or doesn't occur at all.

Let Y be an indicator showing whether a set of genes determining the structure was activated by induction. Three situations are possible for the formation process.

If $X < -C_2$, the reaction is impossible, because the organizer has lost its ability to trigger morhogenesis too early, still before the responding tissue has attained its ability to differentiate ($Y = 0$).

If $-C_2 \leq X \leq C_1$, the formations of the organizer and responding tissue more or less coincide in time, therefore morphogenesis takes place ($Y = 1$).

If $X > C_1$, the reaction is impossible, because the organizer has attained its ability to trigger morphogenesis too late, already after the responding tissue has lost its ability to differentiate ($Y = 0$).

Suppose X to be a quantitative trait determined by multiple additive genes and distributed in a population normally with a mean μ_X and additive genetic variance σ_X^2 in the appropriate scale of measurement. These assumptions do not restrict the generality of the model to a great extent, because certain scale transformations can substantially increase the similarity between empirical and normal distributions (Falconer, 1985).

The proportion of organisms, in which the induction has taken place, can be defined using the formulation of the integral of normal distribution probability as:

$$P = P(Y=1) = P(-C_2 \leq X \leq C_1) = \frac{1}{\sigma_X\sqrt{2\pi}} \int_{-C_2}^{C_1} \exp\left(-\frac{(X-\mu_X)^2}{2\sigma_X^2}\right) dX . \qquad (1)$$

The trait Y is influenced by X and thus can be studied as a threshold character that is the discrete trait determined with a latent continuously varying parameter (Falconer, 1985). A trait with such pattern of variation is a Bernoulli variable with expected value $\mu_Y = P$ and variance $\sigma_Y^2 = P(1-P)$ (Statistics, 1989).

The duration of evolution processes, t, is measured in this paper in discrete generations, meaning that peculiarities of life cycles and repeated reproductions seem not to essentially influence the genetic and phenotypic structures of the population. Assume, that the investigated structure was established and maintained by natural selection in the past ($t < 0$), however after the environmental change in generation $t = 0$ this structure loses its adaptive value. It is supposed that this trait became useless but not deleterious, and could not be an object of direct or indirect negative selection. Therefore, during the time period $t > 0$ exclusively mutation and random genetic drift determine the dynamics of a given trait.

Consider this dynamics in more detail. Character X was defined as a normally distributed quantitative trait determined by multiple additive factors. The dynamics of such characters in neutral evolution has been investigated (Kimura, 1965; Lande, 1976 a, b; Turelli, 1984; Lynch, Hill, 1986; Turelli et al., 1988; Felsenstein, 1988; Bürger et al., 1989; Bürger, Lande, 1994; Martins, 1994). If it is assumed that the population is sufficiently large to ignore random genetic drift and the effects restricting randomness of mating are insignificant, then the dynamics of such a trait should be determined exclusively by the accumulation of

neutral mutations. Major mutations are not analyzed here because their deleterious effects on development are well known (Korochkin, 2002). Only effects of minor mutations are included to the model.

In any generation $t > 0$ the distribution of X should remain normal with the expected value:

$$\mu_X(t) = \mu_X(0), \tag{2}$$

and additive variance:

$$\sigma_X^2(t) = \sigma_X^2(0) + t\tilde{\sigma}_X^2, \tag{3}$$

where $\tilde{\sigma}_X^2$ is the new additive variance introduced by mutation during a generation (Kimura, 1965; Lande, 1976 a). This input is assumed to be unchanged during the period of time under study. Thus, in an infinite population the mean value of normally distributed and additively determined characters remains constant while its variation increases without limits due to the accumulation of random mutations.

A different trend is expected for finite population (Lande, 1976 b; Lynch, Hill, 1986; Turelli et al., 1988). It is important to note that for macroevolutionary periods of time any group must be considered as having finite size (Turelli et al., 1988). In this case mutation increases the trait variance, however random genetic drift decreases it. Sooner or later additive variance achieves equilibrium value

$$E(\sigma_X^2(t)) = 2N_E\tilde{\sigma}_X^2, \tag{4}$$

where N_E is the effective population size (Turelli et al., 1988) and then drifts around this expectation. The expected time span for achieving the equilibrium value (4) is approximately $4N_E$ generations (Turelli et al., 1988). It does not depend on the initial value of the variance (Turelli et al., 1988). In a finite population $\mu_X(t)$ is a random variable distributed normally with expected value:

$$E(\mu_X(t)) = \mu_X(0), \tag{5}$$

and variance:

$$E(\sigma_{\mu_X}^2(t)) = 2t\tilde{\sigma}_X^2, \tag{6}$$

(Lande, 1976 b; Lynch, Hill, 1986; Turelli et al., 1988). For a population under a mutation — drift equilibrium, the rate of shifting the mean value depends on $\tilde{\sigma}_X^2$, but doesn't depend on N_E (Lynch, Hill, 1986; Turelli et al., 1988).

A value of a complex character depends both on whether the induction had taken place and on additive and non-additive genes activated by induction. As usual several induction processes seem to be necessary to form a complex structure. These complications for the model are analyzed in special sections of this paper.

Results

Dynamics of a threshold character in an infinite population

It is possible to construct a model of evolutionary dynamics for threshold character Y in an infinite population (Dzeverin, 2000). The expected value and variance of Y in generation t is accordingly:

$$\mu_Y(t) = P(t), \tag{7}$$

and

$$\sigma_Y^2(t) = P(t)(1 - P(t)). \tag{8}$$

It is evident from (1) and (3) that P(t) decreases with time and consequently $\mu_Y(t)$ decreases, while $\sigma_Y^2(t)$ at first increases reaching the maximum value when $P(t) = 0.5$ and then also decreases.

In a number of biological studies, the coefficient of variation, $\theta = \sigma/\mu$, is applied as an important measure for the level of variability (Lande, 1977). The standard error of the coefficient of variation in a sample is $S_Q = \frac{Q}{\sqrt{N-1}}\sqrt{0.5 + Q^2} \approx \sqrt{\frac{Q^2}{2N}}$, where Q is the sample estimate of the coefficient of variation, and N is the sample size (Lakin, 1990). For a threshold character the coefficient of variation should be a time-dependent function which can be expressed as

$$\theta_Y(t) = \frac{\sigma_Y(t)}{\mu_Y(t)} = \frac{\sqrt{P(t)(1-P(t))}}{P(t)} = \sqrt{\frac{1-P(t)}{P(t)}}. \tag{9}$$

It is clear that, as P(t) decreases, the coefficient of variation increases achieving with time an arbitrarily high value.

These results are illustrated on a numerical example by the fig. 1 and 2. The latent parameter X is supposed to be determined by purely additive genes. Its initial mean

value is $\mu_X(0)=0$, the initial variance is $\sigma_X^2(0)=1$, the new additive variance emerged during a generation is $\tilde{\sigma}_X^2=10^{-3}$, and the threshold limits both are $C_1 = C_2 = 4.0$ in the accepted scale of measurement. Probabilities for successful developmental induction of the threshold character, Y(X), in an infinite population are shown in the figure 1. At the initial state the probability for successful induction is $(1-10^{-4})$ (fig. 1, A). After 10^4 generations this probability in the same population is 0.77 (fig. 1, B). After $2 \cdot 10^4$ generations it is 0.62 (fig. 1, C) and after $4 \cdot 10^4$ generations it is only 0.47 (fig. 1, D). The dynamics of the threshold character, Y(X), in an infinite population is shown in the figure 2: 1 is mean value, $\mu_Y(t)$, 2 is variance, $\sigma_Y^2(t)$, and 3 is coefficient of variation, $\theta_Y(t)$. Time intervals are measured in generations.

Dynamics of a threshold character in populations with limited sizes

The evolutionary dynamics of a threshold character Y determined with latent character X is evident since we know the dynamics of X as a quantitative character (see above). Its variance stabilizes at a low level and is being maintained by new mutations while the mean value drifts in an arbitrary direction. In a finite population there is a high probability that this drift of mean values $\mu_X(t)$ should shift a population out of the limits of the area $-C_2 \le X \le C_1$, in which the formation of the trait is possible (Y = 1). Denote the magnitude of the shift of the mean after t generations by $D_X(t)=|\mu_X(t)-\mu_X(0)|$. The expected value of this variable is

$$E(D_X(t))=\sqrt{2t\tilde{\sigma}_X^2} = \tilde{\sigma}_X\sqrt{2t}, \qquad (10)$$

From here an expected number of generations necessary to deviate from the initial value $\mu_X(0)$ by a distance D_X is

$$E(t(D_X))=\frac{D_X^2}{2\tilde{\sigma}_X^2}, \qquad (11)$$

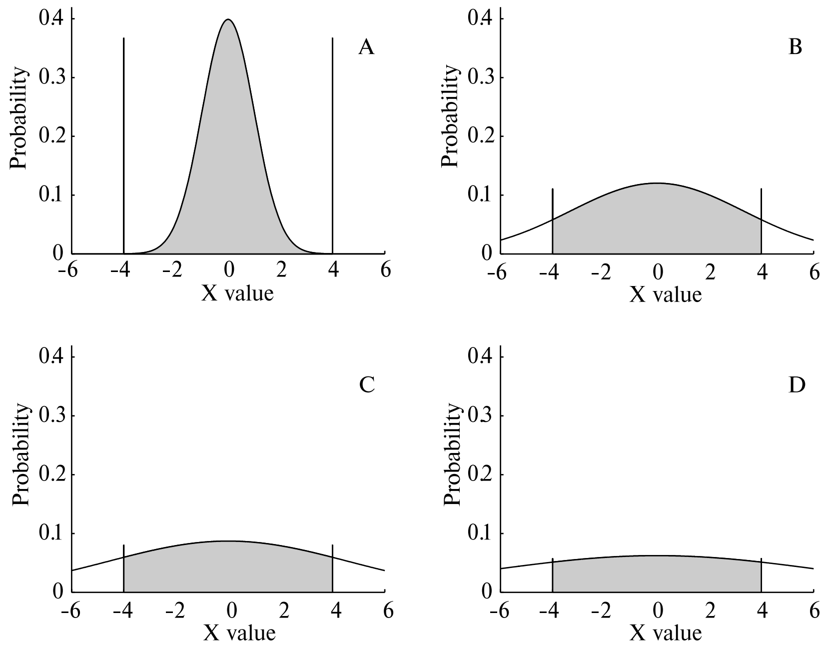


Fig. 1. Probabilities for successful developmental induction of the threshold character in an infinite population. The explanations are in the text.

Рис. 1. Вероятности успешной индукции порогового признака в онтогенезе для бесконечно большой популяции. Обозначения в тексте.

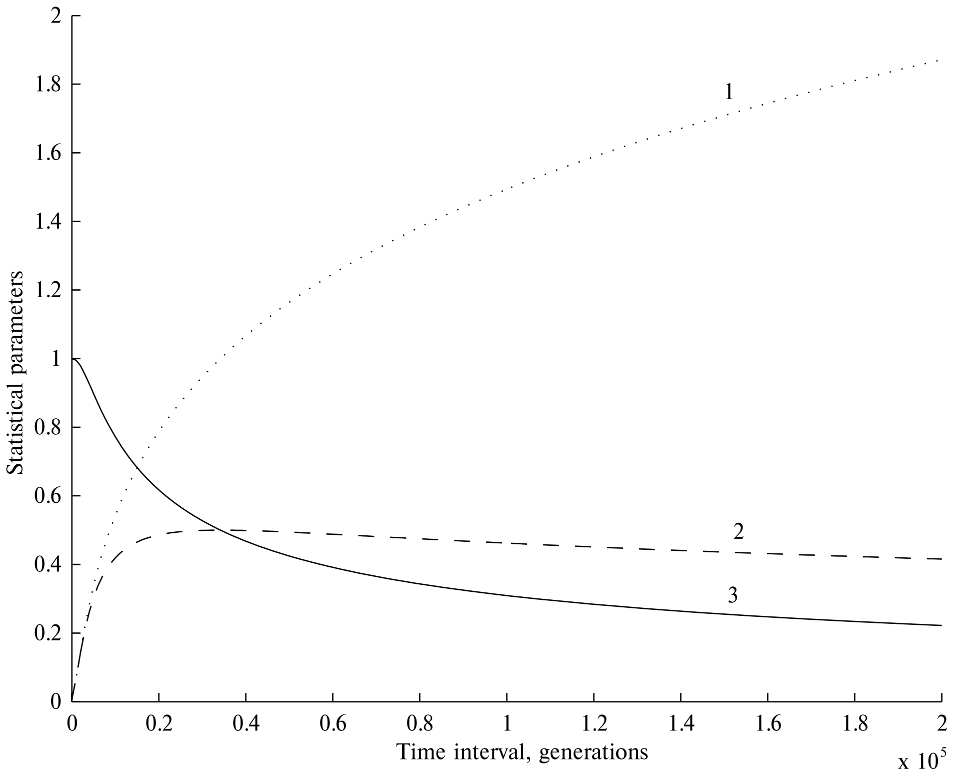


Fig. 2. Dynamics of the statistical parameters of the threshold character in an infinite population. The explanations are in the text.

Рис. 2. Динамика статистических параметров порогового признака для бесконечно большой популяции. Обозначения в тексте.

Thus, most likely, the mean, μ_X, deviates from the initial value to an area, in which the interaction of the responding tissue and organizer is impossible, and the formation of the organ cannot take place.

Assume a sample of replicate populations starting their evolutionary transformations from the same point $\mu_X(0)$. For each population μ_X deviates from this point (at an average, μ_X increases in a half of the sample, and, in a half, it decreases). Within-population variances stabilize while the between-population variance and coefficient of variation increase owing to divergence of population means. Thus, a proportion of populations, which crossed the area $-C_2 \leq X \leq C_1$ gradually increases. For more and more populations the mean value of Y exceeds 0. After a long period of time only some populations preserve the studied character. If population extinctions are independent from value (which follows from the assumed condition of the neutrality of this character), then during a long time a character can be lost by all populations in a group.

An example of neutral dynamics of the statistical parameters of the threshold character Y(X) in a finite-sized population is shown in the figure 3. Mutation — drift equilibrium is assumed for all modeled period. Effective population size, N_E, is 500. An analyzed time period is $1.2 \cdot 10^5$ generations. The consecutive estimates of population structures and statistical parameters are got with intervals of 10^4 generations. For each consecutive step, a mean X value with 99.9% confidence limits of variation, $\mu_X(t) \pm 3.29 \cdot E(\sigma_X(t))$, and frequency of successful induction, $P(Y(X(t)) = 1)$, are estimated. The new additive variance emerging during a generation is $\tilde{\sigma}^2_X = 10^{-3}$, and the threshold limits both are $C_1 = C_2 = 4.0$ in the accepted scale of measurement. The zone

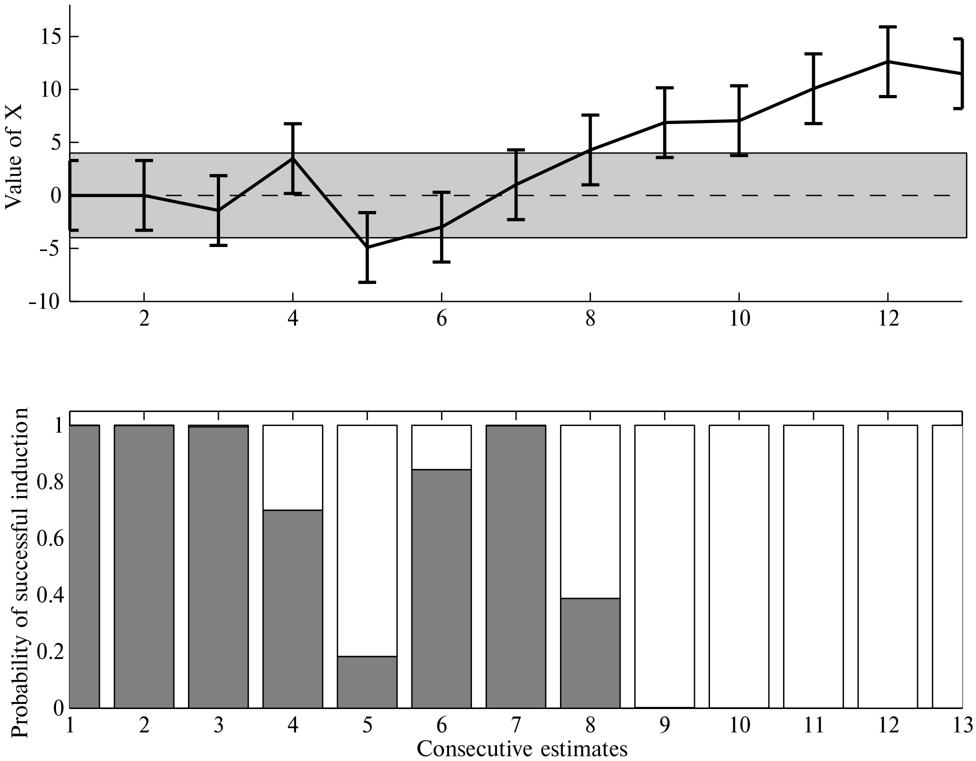


Fig. 3. An example of neutral dynamics of the statistical parameters of the threshold character in a finite-sized population. The explanations are in the text.

Рис. 3. Пример нейтральной динамики статистических параметров порогового признака для популяции конечного размера. Обозначения в тексте.

between these limits is marked with grey color, the initial mean value, $\mu_X(0)$, is marked with a dashed line.

An example of neutral dynamics of the statistical parameters of the threshold character Y(X) in a set of replicate populations is shown in the figure 4. A mutation — drift equilibrium is assumed for all modeled period. Time is measured in generations. The consecutive estimates of mean values are shown at the intervals of 100 generations. New additive variance emerged during a generation is $\tilde{\sigma}_X^2 = 10^{-3}$. The threshold limits both are in the accepted scale of measurement, and the zone between these limits is marked with grey color. The drift of mean values, $\mu_X(t)$, in 10 replicate populations (fig. 4, A) and the dynamics of between-group standard deviation, $\sigma_{\mu_X}(t)$ (fig. 4, B) are modeled.

A threshold character determination by multiple inductions

For many complex organs it is known that multiple consecutive or simultaneous induction processes form them. Previous induction is necessary for the next induction and without a whole series of inductions an organ remains under-developed. As a rule, a series of inductions takes place, and the responding tissue of the previous induction becomes the organizer in the next induction (Hadorn, Wehner, 1989). For example, no less than three or four induction processes occur in the embryogenesis of vertebrates. Primary induction determines general topography of systems of organs; the secondary induction determines the development of organs, while the next inductions control the formation of organ components (Hadorn, Wehner, 1989).

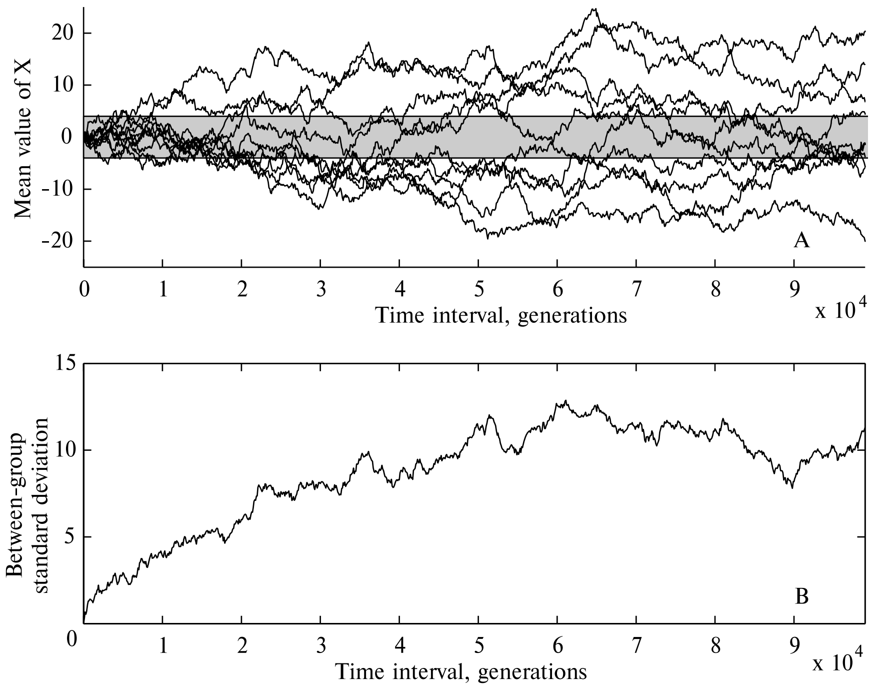


Fig. 4. An example of neutral dynamics of the statistical parameters of the threshold character in a set of 10 replicate populations. The explanations are in the text.

Рис. 4. Пример нейтральной динамики статистических параметров порогового признака в 10 идентичных популяциях с идентичными исходными свойствами. Обозначения в тексте.

To take into account the necessity of multiple inductions for the development of organ (for consecutive inductions, particularly) the proposed model can easily be extended to multiple latent traits, initializing the beginning of development in some volume of the multidimensional timing space. As the number of traits increases, the probability for occuring within the multidimensional hyper-volume decreases with the number of traits.

In the simplest system only two induction processes form an organ. Consider a threshold character formed by two developmental inductions, A and B. Induction indicators, Y_A and Y_B, depend on latent quantitative characters, X_A and X_B, respectively. The mechanism of character determination is the same as described above. A product $Y = Y_A Y_B$ can model a formation of such a character.

If Y_A and Y_B are statistically independent, the mean value and variance of a trait are respectively (Statistics, 1989):

$$\mu_Y = \mu_A \mu_B = P_A P_B \tag{12}$$

and

$$\sigma_Y^2 = \sigma_A^2 \sigma_B^2 + \mu_A^2 \sigma_B^2 + \mu_B^2 \sigma_A^2 = \mu_A^2 \mu_B^2 (\theta_A^2 + \theta_B^2 + \theta_A^2 \theta_B^2). \tag{13}$$

Here $\mu_A = \mu_{Y_A}$, $\sigma_B^2 = \sigma_{Y_B}^2$, etc., while P_A and P_B are the probabilities of A and B. They are the analogues of P in equation (1). It is evident that the expression in brackets is an estimate for the squared coefficient of variation of Y. Thus,

$$\theta_Y = \sqrt{\theta_A^2 + \theta_B^2 + \theta_A^2 \theta_B^2}. \tag{14}$$

If Y_A and Y_B are not independent, a coefficient of correlation between these variables is

$$\varphi = \frac{P_{AB} - P_A P_B}{\sqrt{P_A P_B (1 - P_A)(1 - P_B)}}, \tag{15}$$

where P_{AB} is the proportion of organisms, in which both inductions have taken place. If X_A and X_B jointly follow bivariate normal distribution with mean vector $\begin{pmatrix}\mu_A\\ \mu_B\end{pmatrix}$ and covariance matrix $\begin{pmatrix}\sigma_A^2 & \sigma_A\sigma_B\rho\\ \sigma_A\sigma_B\rho & \sigma_B^2\end{pmatrix}$, then

$$P_{AB}=\frac{1}{2\pi\sigma_A\sigma_B\sqrt{1-\rho^2}}\iint_U f(X_A,X_B)dX_A dX_B, \tag{16}$$

where

$$f(X_A,X_B)=\exp\left(-\frac{\left(\frac{X_A-\mu_A}{\sigma_A}\right)^2+\left(\frac{X_B-\mu_B}{\sigma_B}\right)^2-2\rho\frac{(X_A-\mu_A)(X_B-\mu_B)}{\sigma_A\sigma_B}}{2(1-\rho^2)}\right),$$

and U is a rectangle limited with the conditions: $-C_{A2}\leq X_A\leq C_{A1}$ and $-C_{B2}\leq X_B\leq C_{B1}$. General trends in evolution of phenotypic correlation need special investigation.

Taylor series can be used to obtain reasonable approximations for the parameters of distribution of (Statistics, 1989; Lande, 1977; Manly, 1985). These estimates can be applied if the deviation of data around a mean value is not too large, $Q < 0.1$, that is for analyzing the early stages of regressive processes. Using the first two terms of the Taylor series the approximation gives

$$\mu_Y\approx\mu_A\,\mu_B=P_AP_B, \tag{17}$$

$$\sigma_Y^2\approx\mu_A^2\sigma_B^2+\mu_B^2\sigma_A^2+2\varphi\mu_A\mu_B\sigma_A\sigma_B=\mu_A^2\,\mu_B^2\left(\frac{\sigma_A^2}{\mu_A^2}+\frac{\sigma_B^2}{\mu_B^2}+2\varphi\frac{\sigma_A\sigma_B}{\mu_A\mu_B}\right), \tag{18}$$

and

$$\theta_Y^2\approx\frac{\sigma_A^2}{\mu_A^2}+\frac{\sigma_B^2}{\mu_B^2}+2\varphi\frac{\sigma_A\,\sigma_B}{\mu_A\,\mu_B}=\theta_A^2+\theta_B^2+2\varphi\theta_A\theta_B. \tag{19}$$

The dynamics of correlated threshold characters does not differ essentially from the dynamics of independent threshold characters. Using the equations (7) — (9), the character mean and variance for a population considered infinite can be evaluated respectively as

$$\mu_Y(t)=P_A(t)\,P_B(t) \tag{20}$$

and

$$\sigma_Y^2(t)=P_A^2(t)P_B^2(t)\,\theta_Y^2(t), \tag{21}$$

Thus, the mean value of a product of two threshold characters decreases, and the variance increases at first and decreases later owing to the decreasing of the proportion of specimens having the studied organ developed.

The coefficient of variation of Y also increases (14) or (19) both by increasing variation in Y_A and Y_B, especially if these characters are positively correlated. High negative correlation can slow down this process. The coefficient of variation of Y increases faster than coefficients of variation of its components, Y_A and Y_B.

These results easily can be extended for a threshold character determined by multiple inductions. In this case, the indicator of character formation can be described as $Y=\prod_j Y_j$ (each Y_j is 0 or 1).

Induction effects and the inputs of the additive genes to the value of a quantitative character

Denote a character Z as a product of threshold indicator Y and normally distributed character W, where Y can be an indicator of multiple inductions as has been described in previous section. These components may reflect a developmental mechanism of character initialization and the input from the genes, which had been activated by the

induction. If W and Y are independent, the mean value, variance, and squared coefficient of variation for Z are (Statistics, 1989):

$$\mu_Z = \mu_Y \mu_W = P_Y \mu_W, \quad (22)$$

$$\sigma_Z^2 = \mu_Y^2\sigma_W^2 + \mu_W^2\sigma_Y^2 + \sigma_Y^2\sigma_W^2 = \mu_Y^2\mu_W^2\left(\frac{\sigma_Y^2}{\mu_Y^2} + \frac{\sigma_W^2}{\mu_W^2} + \frac{\sigma_Y^2\sigma_W^2}{\mu_Y^2\mu_W^2}\right), \quad (23)$$

and

$$\theta_Z^2 = \frac{\sigma_Y^2}{\mu_Y^2} + \frac{\sigma_W^2}{\mu_W^2} + \frac{\sigma_Y^2\sigma_W^2}{\mu_Y^2\mu_W^2} = \theta_Y^2 + \theta_W^2 + \theta_Y^2\theta_W^2. \quad (24)$$

If Y and W are correlated, the approximate formulations for the mean value, variance, and coefficient of variation of Z can be obtained using the Taylor series like in the equations (17) — (19).

The dynamics of a trait Z in neutral evolution can be described using the data on dynamics of Y and W. The dynamics of the threshold indicator has been described by the equations (7) — (9), while W is a normally distributed quantitative character, and its dynamics corresponds to equations (2) — (3). Using (22) and (23) character mean and variance can be evaluated respectively as

$$\mu_Z(t) = P(t)\,\mu_W(t) = P(t)\,\mu_W(0), \quad (25)$$

and

$$\sigma_Z^2(t) = \mu_Y^2(t)\mu_W^2(t)\theta_Z^2(t) = P^2(t)\mu_W^2(0)\theta_Z^2(t), \quad (26)$$

For quantitative character W the amount of variation in a generation t is

$$\theta_W(t) = \frac{\sigma_W(t)}{\mu_W(t)} = \frac{\sqrt{\sigma_W^2(0) + t\tilde{\sigma}_W^2 + \breve{\sigma}_W^2}}{\mu_W(0)}, \quad (27)$$

where $\tilde{\sigma}_W^2$ is new additive variance produced for W by mutation during a generation and $\breve{\sigma}_W^2$ is variance formed by environmental and other non-additive factors. In this case the coefficient of variation also increases with time. The coefficient of variation of Z also increases (24) both by increasing of the variation of Y and by the increasing of variation of W. Negative correlation between Y and W can slow down this process.

These results can be extended for modeling a character determined by various combinations of consecutive and simultaneous inductions. The mean value of such a character diminishes in neutral evolution due to both increasing the frequency of specimens in which the character is not being formed and reducing its size in organisms with this character being manifested. The discovered effects (enhanced variation of more complicated structures, simplification of such structures and diminishing size, decreasing proportion of specimens having this structure even in vestigial state) take place in groups of replicate populations of finite sizes, too. Such modeling can be used as a representation for the dynamics of a degenerating character in a major taxon subdivided into a number of species or other subgroups. Therefore introducing the multiple inductions effects and additive genes inputs to the value of a quantitative character seems to have made the proposed model more reliable without changing the general pattern of neutral regressive evolution. Quantitative characters with such mechanisms of determination tend to be reduced in the evolutionary prospect, too.

Examples

Some examples with empirical data

Patterns of variation in vestigial structures. — The regressive changes of vestigial organs in comparison with their fully functional homologues are illustrated here using the data on skeletal and first of all dental structures of some fossil and recent mammals.

Typically the coefficient of variation for functional skeletal elements in mammals exceeds 0.03—0.10 (Simpson, 1944; for detailed statistics see Yablokov, 1966). Increa-

sed variation had been detected for functionally unused structures. According to Simpson, "it is so commonly true that degenerating structures are highly variable that this may be advanced as an empirical evolutionary generalization" (Simpson, 1944: 39). For example, the vestigial third upper premolar tooth, $P^3/$, was highly variable ($Q = 0.185 \pm 0.028$), in Ptilodus montanus (Multituberculata, Paleocene of North America) while well-developed teeth had a typical level of variability ($Q = 0.057 \pm 0.014$ for the length of the first lower molar, $M/_1$) (Simpson, 1944: 39). Another vestigial tooth, the second upper premolar, $P^2/$, in *Hoplophoneus* (Carnivora, Felidae, Oligocene of Asia and North America) was highly variable, too, with asymmetrical formation, and could be missing in some specimens (Simpson, 1944: 39).

The second upper molar, $M^2/$, is supposed to degenerate in the evolution of Hyaenidae. In *Ictitherium hyaenoides* (Hyaenidae, Neogene, China) $M^2/$ was very variable and highly reduced (population mean, M, is 5.4 ± 0.28, $Q = 0.136 \pm 0.036$) in comparison with $M^1/$ ($M = 15.9 \pm 0.34$, $Q = 0.88 \pm 0.015$) and could be absent in some specimens (Kurtén, 1953). Another species of *Ictitherium* had normally developed $M^2/$, while in the modern species *Crocuta variabilis* $M^2/$ is missing and $M^1/$ is vestigial (see Kurtén, 1953 for details). Premolars of *Ursus arctos* (Ursidae) demonstrate a similar pattern of variation. They are more or less vestigial and any of them may be missing (Kurtén, 1953). For many groups of mammals it had been shown that teeth which are phylogenetically lost might occasionally be realized once more (see Kurtén, 1953 for discussion).

The extreme variation and little correlation with other limb bones had been revealed for first phalanx of second wing digit in *Myotis lucifugus* and *M. sodalis* (Chiroptera, Vespertilionidae) (Bader, Hall, 1960). This bone has little functional significance for the bat wing, so this fact "clearly indicates that the factors which normally operate to control or limit bone development are absent, or at least greatly modified, with respect to this element. The almost complete absence of significant correlation between the phalanx and all other skeletal parts is corroborative evidence. Such variation is common in aspects of the skeleton or dentition which are non-functional and presumably under greatly relaxed selective control" (Bader, Hall, 1960: 15).

However, in some cases this typical relation between variation and performance has not been revealed. Thus, in the teeth of *Viverravus acutus* and the *Didymictus proteus — protenus* complex (Viverravidae, Carnivora, Paleogene of North America) those cusps that should be functionally constrained are actually the most variable (Polly, 1998). The pattern of their variability is better explained by developmental factors than by the direct action of natural selection (Polly, 1998). Some correlations between limb bones in *Myotis* can be explained as being formed by developmental factors, too (Bader, Hall, 1960).

Evolution of third upper premolars in bats as an example of a regressive trend. — The evolutionary trends of dental characters in bats are studied in details (Menu, 1985, 1987; Wołoszyn, 1987). In particular, the third upper premolar ($P^3/$) is degenerating in various groups of Chiroptera. Its regressive trend started from a quite well developed state in primitive Paleogene bats, for example, *Icaronycteris* (Jepsen, 1966) and *Stehlinia* (Sigé, 1974). Later the proportion of genera with underdeveloped $P^3/$ increases. This tooth is missing in the majority of modern bat genera while the species of *Myotis* genus have vestigial $P^3/$ with evident features of under-development (Menu, 1985, 1987). Contrary to other vespertilionid bats, *Pizonyx vivesi*, a bat closely related to *Myotis*, has relatively larger $P^3/$ (Menu, 1985).

The under-development of $P^3/$ in *Myotis* is expressed by diminishing, simplification, and lateral exclusion from the toothrow (Menu, 1985, 1987; Dzeverin, 2001). Already in the fossil species, *M. bavaricus* from Miocene of Central Europe, the length of $P^3/$ was more variable ($Q = 0.066$ for one sample, and $Q = 0.075$ for another) com-

pared to lengths of M/$_1$ (Q exceeds 0.034 and 0.037, respectively) and M/$_2$ (0.035 and 0.042) (Ziegler, 2003). In modern *Myotis* species all stages of P^3/ degeneration span from almost normally developed, for example, in *M. bechsteinii*, *M. ikonnikovi,* up to completely absent in *M. ridleyi* and *M. rosseti* (Hill, Topál, 1974; Menu, 1985, 1987; Dzeverin, 2001). High intraspecific variation of P^3/ size is known as well (Hill, Topál, 1974; Menu, 1985, 1987; Dzeverin, 2001). Moreover, these teeth can be absent in separate specimens of a number of *Myotis* species (Strelkov, 1983; Dzeverin, 2001; Ghazali, Dzeverin, 2004). In *M. blythii* P^3/ is absent on one or both sides of the toothrow nearly in 1.4% of individuals (Dzeverin, unpublished data).

For three *Myotis* species (*M. myotis*, *M. blythii*, and *M. mystacinus* s. l. from the East Europe) coefficients of variation of the measurements of under-developed teeth reach 10—40% or even more, that is several times higher than the variability of well-developed teeth. The height of P^3/ turned out to be the most variable character. The largest coefficient of variation had been found for *M. mystacinus* ($Q = 0.65$, $S_Q = 0.18$), the least ones have been recorded in *M. blythii* ($Q = 0.39$, $S_Q = 0.09$), and *M. myotis* ($Q = 0.42$, $S_Q = 0.09$) (Ghazali, Dzeverin, 2004). On the contrary, fully functional M/$_1$ is less variable both in *M. mystacinus* ($Q = 0.22$, $S_Q = 0.046$), *M. blythii* ($Q = 0.12$, $S_Q = 0.029$), and *M. myotis* ($Q = 0.23$, $S_Q = 0.044$) (Ghazali, Dzeverin, unpublished data). The extremely high range of variation of P^3/ in *M. mystacinus* agrees with the well-known data on the high level of degeneration of this tooth in this species (Strelkov, 1983).

Numerical estimations

Most of the variables used in this paper have been estimated for numerous animal and plant populations (Falconer, 1985; Hedrick, 2000). Statistical estimates for the main components of variance are not too diverse. Assuming N_E = 500 individuals, the new additive variance per generation being nearly 10^{-3}—10^{-4} of non-additive variance, and narrow-sense heritability nearly 0.5 is quite realistic for many purposes (Hedrick, 2000). The probability for ceasing the development of a fully functional character, $P(Y(t = 0)) = 0$, can be estimated as being of the order of 10^{-3} or somewhat lesser for late inductions, that is for final stages of organ's development.

Consider effective population size, $N_E = 500$, the new additive variance, $\tilde{\sigma}_X^2 = 10^{-3}\sigma_X^2(0)$, and threshold limits, $C_1 = C_2 = 4.0 \cdot \sigma_X(0)$, as estimates for a threshold character, $Y(X(t))$, in a population under mutation — drift equilibrium. In such a population the additive variance of X should be roughly constant with an average value of $E(\sigma_X^2(t)) = 2N_E\,\tilde{\sigma}_X^2 = \sigma_X^2(0)$. At an initial point there is a fairly reliable mechanism for developmental induction, $P(Y = 1) = (1-10^{-4})$. But later, under the conditions of selective neutrality and random drift, the population mean should deviate to a zone in which this induction is not possible. The expected time for such a drift can be estimated from the equation (11) as 32000 generations to drift away for 8 standard deviations, and 50000 generations — to drift away for 10 standard deviations, etc. (confer with fig. 3 and 4). Assuming $\tilde{\sigma}_X^2 = 10^{-4}\sigma_X^2(0)$ implies ten times more intervals, that is 320 000 and 500 000 generations for previous examples.

Since a generation period for numerous animals comprises nearly a year, these time intervals are much smaller than periods of macroevolutionary changes revealed from paleontologic data. These estimates concern the simplest model of a character maintained by only a single induction. Characters formed by consecutive inductions should reduce still even faster (see equations (12) — (21)). If to consider a population as being infinitely large, the estimated rate of degeneration is comparable with empirical data on evolutionary regressive processes (Dzeverin, 2000). However, for populations with limited size, various types of threshold characters described above are expected to degenerate and vanish in the course of neutral evolution very quickly comparing

with the macroevolutionary scale of time. This result agrees with Yablokov's (1966) hypothesis that common vestigial organs really are fully functional, because genuine useless organs should rapidly degenerate without selection control. Only atavistic organs can be supposed to be really useless from this standpoint (Yablokov, 1966). For many deleterious structures selection seems not to be necessary: mutation destruct them quicker (Schmalhausen, 1982).

Paleontologic studies have demonstrated that there is a great variety in rates of regressive changes of morphological characters, and very often these rates are very small. For example, in evolution of vespertilionid bats, $P^3/$ had been lost in numerous bat genera at early stages of their evolution (probably in Oligocene and Miocene, when these genera were emerging). But in *Myotis* the regressive evolution of this tooth continues up to the present time, extending dozens times more than the period implied by the quantitative modeling. Some other teeth demonstrate similar prolonged trends in these genera, too. Certain functional value and genetic correlation with important structures are the most probable mechanisms that could prevent the rapid loss of vestigial structures.

Discussion

Principal features of typical regressive processes are reproduced in the model developed in this paper. Reducing the probability of developmental induction is reflected in equations (1), (7), and fig. 1, 2, and 3. Equations (8), (9), (21), (26), (27) and fig. 2 and 4 reproduce the increase in variation of degenerating character. Thus, taking into account the induction mechanism of character development (equation (1)) and a trend of structural elements to be reduced, it is possible to expect that the diminishing and simplification of an organ will occur by a consecutive loss of its components. Decreasing of its size is described by the equations (20) and (25). The opportunity to re-express lost structures (that is to develop atavisms) is supposed by the model as well. Stochastic trends of the modeled characters in replicate lineages are described by the equations (10) and (11) and illustrated by fig. 3 and 4. Usually these lineages have similar trends for character reduction, but characters degenerate with different rates in different lineages.

It may be suggested from the present results that during purely neutral evolution a character formed by interaction of pre-existing structures gradually reduces and disappears due to disintegration of morphogenetic systems which had to make this interaction possible. Variation of such an organ increases without limits. The disintegration of pattern formation systems occurs from random neutral mutation and stochastic genetic drift. Thus, the directional process of regressive transformation occurs to be the result of indirect random processes.

Selection influence on regressive trends is highly probable for natural populations. The regressive transformations of organs in evolution can be induced by the inactivation or damage of genetic information by random mutation as well as by negative selection. Direct or indirect selection can put the brake to the complete loss of vestigial characters. This is possible if such characters are maintained by indirect selection through pleiotropy with adaptive characters. For example, the genes responsible for the development of hind limbs in cetaceans can be supported by indirect selection due to the genetic correlation either with pelvic bones which serve as points of attachment for urogenital musculature or with front limbs (Yablokov, 1966; Lande, 1978).

On the other hand, loss of a character can be induced by negative selection if the detrimental effect of such a character exceeds any direct or indirect advantages. In a number of cases it is difficult to distinguish between the random effects and selection (Manly, 1985). Nevertheless, the rates of regressive evolution, which can be estimated

from paleontologic data, are rather small and can be maintained either by mutation or by rather weak selection. It is enough for weighted selection differential to be of the order of 10^{-3}—10^{-4} (Lande, 1978).

Thus, a choice between the hypotheses about mutation and selection inputs on the regressive process is a serious problem, which is not yet solved. Only preliminary suppositions may be done. For these trends successful testing may be grounded on the evaluation of character variation. A number of researchers emphasized on a very high amount of variation in vestigial structures (for example, Darwin, 1998; Schmalhausen, 1982; Simpson, 1944; Yablokov, 1966; Lande, 1978; Peters, Peters, 1984) and in other structures of little functional significance (for example, Bader, Hall, 1960). Variation of an organ being transformed by selection decreases, while without selection the variation should increase (Kimura, 1965; Lande, 1976 a, b, 1979; Lynch, Hill, 1986; Bürger, Lande, 1994; and many other authors). Appropriate statistical tests (t-test on standard deviation, coefficient of variation, Levene test, etc.) can show this increase in variation. One of the possible approaches for such testing is the comparison of variation in homologous organs with different evolutionary trends.

The mechanism of organ loss from the misalignment of reactants implies that genes necessary for development are not certainly lost. Typically, the genotype may contain various non-expressed programs for the development of a character, and some evolutionary saltations probably are the results of switching the development over to another program (Mednikov, 1987; Shishkin, 1984).

Vestigial characters can become the grounds for reverse evolution and formations of new characters and structures. The increase of $P^3/$ in the evolution of *Pizonyx* is possibly an example of such a trend. The adaptive meaning for this change is quite unknown. Molecular phylogenetic reconstruction has shown that *Pizonyx vivesi* is in so near relation with New World *Myotis* species that it must be included to this genus (Stadelmann et al., 2004). Ecologically, *Pizonyx* is a specialized representative of the morphological pattern typical for water trawling *Myotis* species from the subgenus *Leuconoe* (Findley, 1972; Dzeverin, 1998; Fenton, Bogdanowicz, 2002). However, *Pizonyx* dentition evidently differs from dentitions of *Leuconoe* as well as other bats (Menu, 1985).

Besides the developmental mechanism described in this paper, some other processes can also increase the phenotypic variation in vestigial characters. In particular, developmental instability can increase the non-additive component of phenotypic variance. As usual, the level of bilateral asymmetry is used as a measure of developmental instability (Van Valen, 1962; Hallgrimsson, 1998 and many others). This approach can be integrated with quantitative genetic analysis of variation and evolution (Gavrilets, Hastings, 1994). Well-developed organs are expected to be more sustainable in their development than under-developed ones. However, for dental characters of *Myotis* species it has been shown that a pattern of bilateral asymmetry differs from a pattern of general variability estimated by the coefficient of variation (Ghazali, Dzeverin, 2004). The least asymmetry was found for *M. mystacinus.* Considerable asymmetry of $P^3/$ was not revealed. This distinction in patterns of variation needs more investigation. It is probable that in many cases high correlation with functional characters slows down the regressive trend of vestigial character (Lande, 1978; Polly, 1998).

However, it is quite probable that correlations of a degenerating character with other characters themselves tend to decrease under regressive trend. This supposition agrees with both Schmalhausen's concept (1982) and empirical data. Fully functional teeth of *Ictitherium* were highly correlated while unused teeth varied more independently from other ones (Kurtén, 1953). A similar correlation pattern of wing bones in *Myotis* (Bader, Hall, 1960) has been already mentioned in this paper. How correlations and

covariations between complex characters can be changed in evolution is a serious and important problem for theoretical studies.

The proposed model can probably be applied not only for investigating vestigial characters. Similar processes of disintegration in interacting structures occur during other evolutionary trends, for example under domestication (Schmalhausen, 1982; Korochkin, 2002). Premature or delayed initialization of development in some tissues or structures may be the basis for transformations in size and shape usually denoted as heterochronies (Hall, 1984; Korochkin, 2002). It had been supposed that alike the random lack of coincidence of reactants may lead to the under-development of certain characters, an opposite event, that is random mutation-induced coincidence of structures which normally do not interact, can be the developmental mechanism for the emergence of new characters (Korochkin, 2002).

The introduction of developmental events to the reconstruction of evolutionary changes has made possible the description of some important features of regressive trends. So far as complex phenotypic structures tend to be reduced by mutation inputs, if stabilizing selection doesn't prevent this, some limitations must be assumed for long-termed neutral changes. Some input of selection is expected to be necessary for organs and other complex structures to stay at the achieved level of complexity.

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